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Substituted 4-hydroxy-1,2,3-triazoles: synthesis, characterization and first drug design applications through bioisosteric modulation and scaffold hopping approaches†

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Bioisosterism and *scaffold hopping* are two widely used approaches in medicinal chemistry for the purpose of lead optimization. The study highlights the physicochemical properties of the 4-hydroxy-1,2,3-triazole scaffold, a less investigated heterocyclic system. Synthetic strategies to obtain different *N*-substituted 4-hydroxy-1,2,3-triazole isomers are presented, and their role as possible isosteres of the carboxylic acid is discussed. The aim is to use this system to modulate the acidic moieties present in lead compounds and, at the same time, to regiodirect substituents in set directions, through targeted substitution on the three nitrogen atoms of the triazole ring. Through this approach, compounds having enhanced binding affinity, will be sought. Two examples of bioisosteric applications of this moiety are presented. In the first example, a classical bioisosteric approach mimicking the distal (S)-glutamic acid carboxyl group using the 4-hydroxy-1,2,3-triazole moiety is applied, to obtain two promising glutamate analogs. In the second example, a scaffold hopping approach is applied, replacing the phenolic moiety present in MDG-1-33A, a potent inhibitor of *Onchocerca volvulus* chitinase, with the 4-hydroxy-1,2,3-triazole scaffold. The 4-hydroxy-1,2,3-triazole system appears to be useful and versatile in drug design.

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Introduction

Bioisosteric replacement and scaffold hopping are two techniques widely used in drug design to enhance potency, selectivity, and other properties of a lead compound, and to find new chemical entities with improved features. These techniques may be defined as replacing part of a bioactive molecule with a substructure that is similar in size and that exhibits similar properties.¹ *Bioisosterism* is an extension of the concept of isosterism in which two functional groups,

known as isosteres, that present similar physicochemical properties, are related. When isosteres also possess a common biological profile, they are known as *bioisosteres*.² Whereas chemistry dictates the isosteric similarity of groups, only the biological target can determine their bioisosteric similarity. *Scaffold hopping* is a subset of the bioisosteric replacement process in which the core structure of a small molecule is replaced. The core may be of direct functional importance in interacting with the biological target, or it may provide the necessary scaffold that allows substitution with functional groups in the appropriate geometric configuration.¹ For the appropriate application of these powerful strategies to drug design, continuous efforts must be made to develop innovative isosteres that meet specific target requirements. An application of bioisosteric substitution as a tool for generating new antidiabetic lead structures using a family of acidic hydroxy-azoles was made in 1995 by a team at Wyeth.³ In that paper, the structure–activity relationship studies determined that the 3-hydroxypirazoles were the most promising new class of potential antidiabetic agent while the 4-hydroxy-1,2,3-triazole ring system was not effective. Although, it must be emphasized that the study was *in vivo* and some unknown

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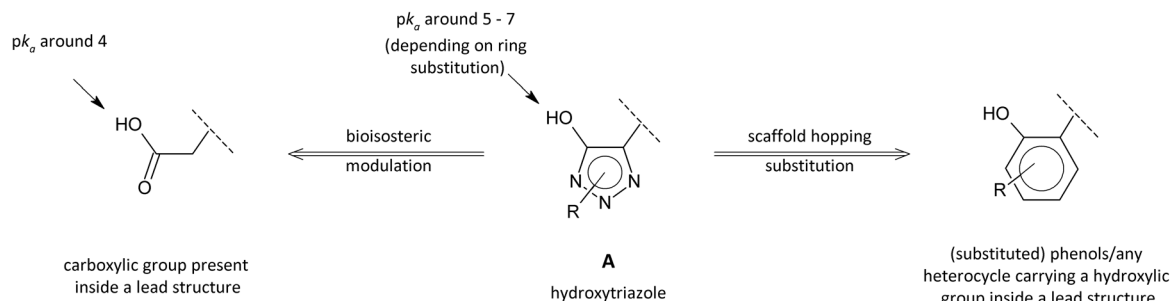


Fig. 1 General structure of the hydroxytriazole system (A). The system may be used both to (bio)isosterically modulate a carboxylic acid (left), mainly thanks to the comparatively low pK_a value of the hydroxyl group, and to substitute a generic hydroxylated (hetero)aromatic ring (right), exploiting a scaffold hopping approach.

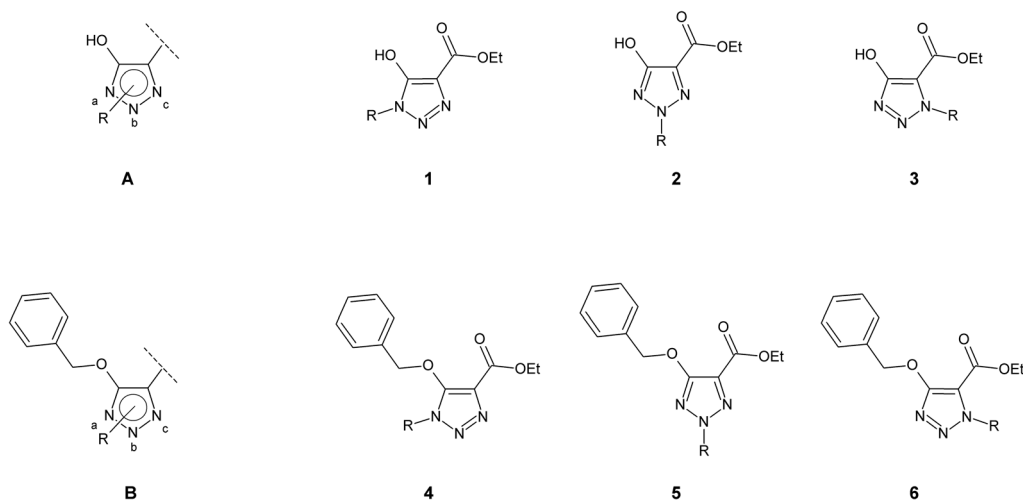


Fig. 2 Hydroxytriazole system (structure A) and its related hydroxytriazole isomers **1**, **2** and **3** together with the benzyl protected forms (general structure B), and related triazole isomers **4**, **5** and **6**. Substitutions on the nitrogen atoms are arbitrarily named *N(a)*, *N(b)* and *N(c)* for easy reference.

mechanism could interfere with the activity of the studied compounds. To our knowledge, no other similar application was subsequently reported on the 4-hydroxy-1,2,3-triazole system.

This study focuses on the bioisosteric application of the pentatomic 4-hydroxy-1,2,3-triazole system (hereafter the *hydroxytriazole* system, structure A, Fig. 1). The attractive feature of this system is the possibility it offers to regiodirect substituents in set directions, by substituting the three nitrogen atoms of the triazole ring; this is absent in other pentatomic heterocyclics (*i.e.* furazan and thiadiazole). Moreover, the carbon substituent offers the potential to modulate the pK_a of the hydroxyl moiety. This approach might be used to explore additional binding areas during bioisosteric applications. Because of its versatility, this system can also be employed in *scaffold hopping*, for example it is well suited to replace a generic hydroxylated aromatic ring (Fig. 1).

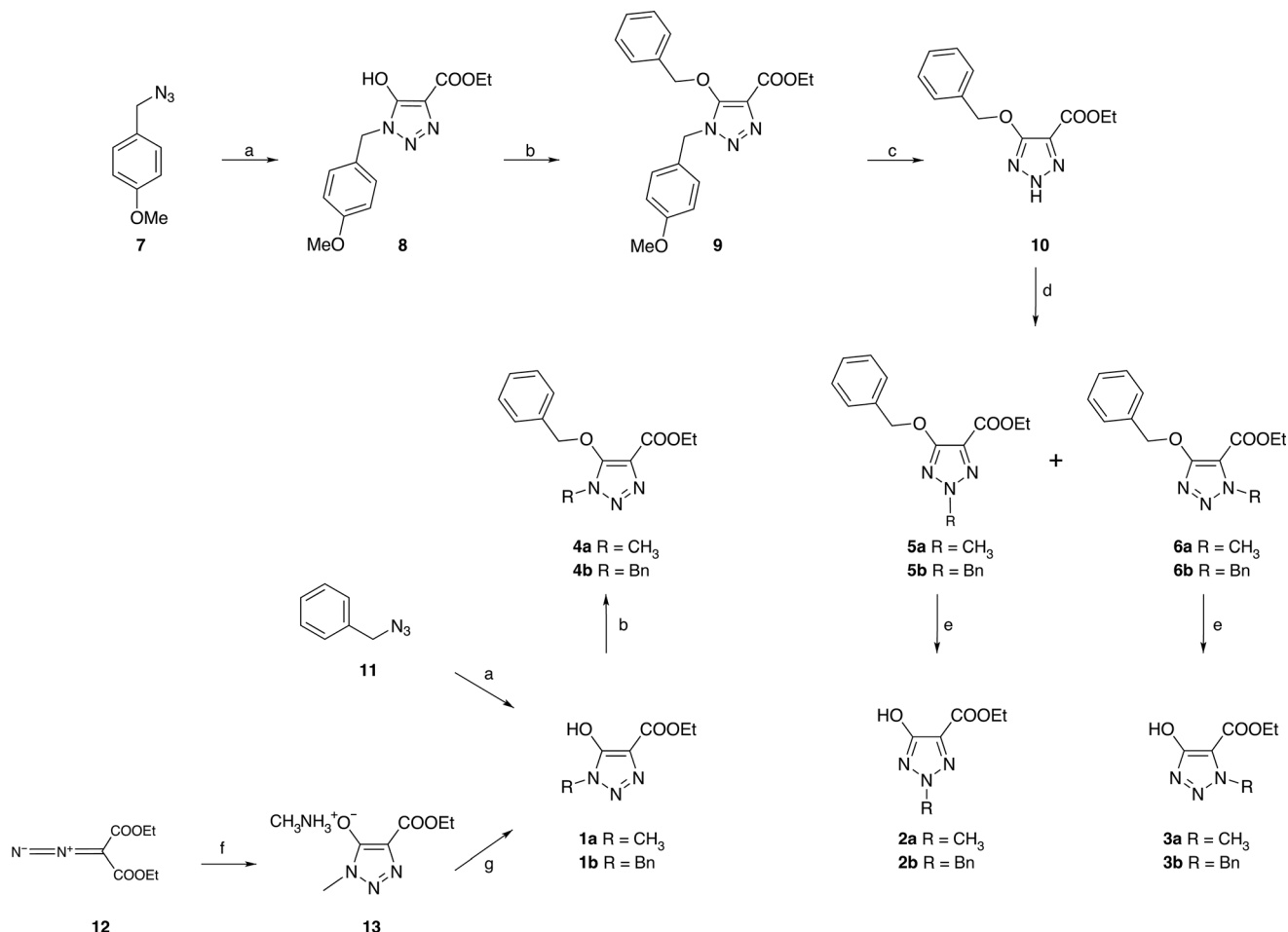
This article presents and rationalizes the synthetic strategy to obtain different *N*-regio-substituted 4-hydroxy-1,2,3-triazoles. Structural characterization and physicochemical properties (pK_a and $ClogP$) of some *N*-substituted isomeric hydroxytriazoles are also presented. This preparatory study

lays the foundation for future exploitation of hydroxytriazoles as bioisosteres of acidic functions. We also present two successful bioisosteric applications using this moiety. The first is an example of a classical *bioisosteric application*, in which the hydroxytriazole system was successfully used to replace the distal carboxyl group of (*S*)-glutamic acid (Glu), the excitatory neurotransmitter responsible for major neurodegenerative diseases.⁴ The second example is of *scaffold hopping*, in which the hydroxytriazole system was used to replace the phenol ring present in MDG-1-33A, a potent and specific *Onchocerca volvulus* chitinase (OvCHT1) inhibitor.⁵ OvCHT1 is hypothesized to play a key role in the life cycle of the worm parasite responsible for *Onchocerciasis*, a neglected tropical disease claimed to be the world's second leading infectious cause of blindness.

Result and discussion

Chemistry

A straightforward and robust chemical strategy to obtain a series of hydroxytriazole isomers (type A, Fig. 2) is presented.



Scheme 1 Synthesis of differently substituted hydroxytriazoles **1**, **2** and **3** and their protected forms **4**, **5** and **6**; (a) diethyl malonate, EtO^-Na^+ , EtOH, reflux; (b) BnBr, K_2CO_3 , DMF, rt; (c) CAN, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (9/1), rt; (d) R-X, K_2CO_3 , CH_3CN , rt; (e) H_2/Pd , THF, rt; (f) MeNH_2 ; (g) 0.5 N HCl.

The isomers bearing different substituents on the three nitrogen atoms are shown as formulas **1**, **2** and **3** (Fig. 2).

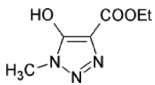
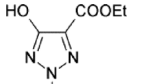
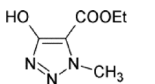
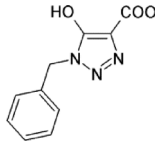
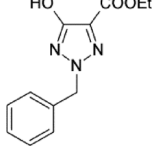
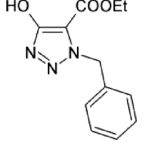
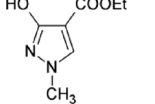
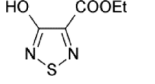
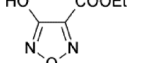
The carboxylate substituent offers additional opportunities for synthetic applications, as it can easily be transformed into other functional groups to link the triazole scaffold to additional molecule portions. The general synthetic scheme to obtain hydroxytriazoles **1**, **2** and **3** is shown in Scheme 1.

4-Methoxybenzylazide **7** first underwent regioselective reaction with diethyl malonate and sodium ethoxide in ethanol, as described by Buckle *et al.*,⁶ to obtain compound **8** (yield 71%). Subsequent treatment of **8** with benzyl bromide in DMF afforded the corresponding *O*-benzyl protected **9** in 55% yield. The structure of **9** was unequivocally assigned using heteronuclear 2D-NMR (HSQC and HMBC) techniques. The results of these studies confirmed the reported regioselectivity of the cycloaddition reaction used to obtain **8**.^{6,7} The 4-methoxybenzyl moiety was selectively removed using cerium ammonium nitrate (CAN) to afford triazole **10** in 35% yield. The reactivity of **10** towards alkylating agents was then investigated. Reaction of **10** with different alkyl and benzyl halides in acetonitrile at room temperature afforded a mixture of two isomers, which was separable by flash

chromatography. Two exemplifying compounds (structures **5** and **6**) are presented in Scheme 1; other examples using different alkyl halides afforded comparable results.⁸ The structures of the three isomeric benzyl derivatives (**4b**, **5b** and **6b**) were assigned by heteronuclear 2D-NMR (HSQC and HMBC). The structure elucidation of these isomeric series will be extensively discussed in a forthcoming full article. The data indicated alkylation reactivity of **10** at both the *N*(b) and *N*(c) ring positions, but not at *N*(a); this is in line with findings reported for other ethyl triazole-4-carboxylates.⁸ In all cases, compounds with structure **5** were obtained in higher yields (47% and 45% for compounds **5a** and **5b**, respectively) compared to compounds with structure **6** (30% for both **6a** and **6b**). Hydroxytriazoles **2** and **3** were obtained from the corresponding *O*-benzylated derivatives **5** and **6** by catalytic hydrogenation at atmospheric pressure pressure in 90% yield in both cases.

To avoid the risk due to the explosive behavior of azides with low C/N ratios, two different synthetic strategies were designed for **1a** and **1b**. For **1a**, diethyl diazomalonate **12**⁹ was treated with methylamine to yield the desired triazole as the primary ammonium salt **13** (yield 79%). After

Table 1 Measured pK_a and $C \log P$ values for compounds **1a–3a**, **1b–3b**, **14–16**

Compound	Structure	pK_a^a	$C \log P^b$
1a		6.21 ± 0.02	0.46
2a		5.14 ± 0.02	0.95
3a		5.54 ± 0.02	0.46
1b		6.22 ± 0.02	2.23
2b		5.14 ± 0.02	2.72
3b		5.38 ± 0.01	2.23
14		6.71 ± 0.01	1.19
15		4.21 ± 0.01	2.09
16		3.24 ± 0.05	1.61

^a Determined by potentiometry (see ESI); each dataset represents mean \pm SD of five independent experiments. ^b Calculated by Biolum for windows v. 1.5, Biobite Corp., Claremont, CA, USA.

acidification and extraction with ethyl acetate, the free hydroxytriazole **1a** was isolated without any further purification (quantitative yield). Conversely, for **1b**, benzylazide was treated with diethyl malonate and sodium ethoxide in ethanol, similar to the preparation of **8** (70% yield). Benzylation of compounds **1a** and **1b** with benzylbromide in dimethylformamide afforded the corresponding *O*-benzyl protected compounds **4a** and **4b** (93% and 83% yield, respectively).

Physicochemical profile and isosteric evaluation

In order to correctly modulate a functional group through a bioisosteric approach, a wide range of isosteric replacements

must be evaluated. The selection should be initially guided by using some important physicochemical parameters such as pK_a or other.¹⁰ Usually being the first to be taken into account in handling acidic isosteres of the carboxyl group, the pK_a value of selected hydroxytriazoles (compounds **1a–b**, **2a–b** and **3a–b**) were measured by potentiometric titration, in order to find a correlation between the hydroxytriazole ring substitution and the pK_a value (Table 1). For comparison purposes, the pK_a values of three other hydroxylated pentatomic heterocyclic systems (hydroxypyrazole **14**, hydroxythiadiazole **15** and hydroxyfurazan **16**) are also given.

Together with dissociation constants, lipophilicity is an important physicochemical parameter that should be taken into account in seeking bioisosterism. To evaluate this effect, the calculated $\log P$ ($C \log P$) values are included in Table 1.

In the hydroxytriazole system, the pK_a value appears to be influenced by substitution on the three endocyclic nitrogens *N*(a), *N*(b) and *N*(c). The *N*(a)-substituted isomers **1a** and **1b** present higher pK_a values (6.21 and 6.22, respectively), similar to that of the hydroxypyrazole (**14**, pK_a = 6.71). *N*(b)- and *N*(c)-substituted compounds (**2a–b**, **3a–b**) are slightly more acidic, with pK_a values in the 5.14–5.54 range. Although less acidic compared to either hydroxythiadiazole **15** (pK_a = 4.21) or hydroxyfurazan **16** (pK_a = 3.24), compounds **2a** and **2b** may still be fully deprotonated at physiological pH. Comparison of $C \log P$ values showed smaller values for the *N*-methyl substituted hydroxytriazoles **1a**, **2a** and **3a** compared to those of compounds **14**, **15** and **16**. Hydroxytriazoles **1a–b**, **2a–b** and **3a–b** may thus be considered potential bioisosteres of a carboxylic acid, since they exist predominantly in their deprotonated states at physiological pH.

Examples of successful bioisosteric application of the hydroxytriazole moiety

The first application presented here is an example of a classical bioisosteric modulation, in which the carboxylic acid of a lead compound is replaced with a series of isosteric moieties. The biological activities of the resulting compounds are evaluated to determine the best bioisostere. The compound selected for modulation is a natural compound, (*S*)-Glu, for which specific agonists and antagonists are necessary in order to characterize the physiological and pathological roles of the different types of glutamate receptors (GluRs).^{11,12}

In the second application, the potent OvCHT1 inhibitor MDG-1-33A was modulated.⁵ The lack of any crystallographic data makes this a challenging task, as such data would be useful to guide the rational design of inhibitors. By modulating the triazole scaffold substitution, an advantageous positioning of the lipophilic substituent was achieved.

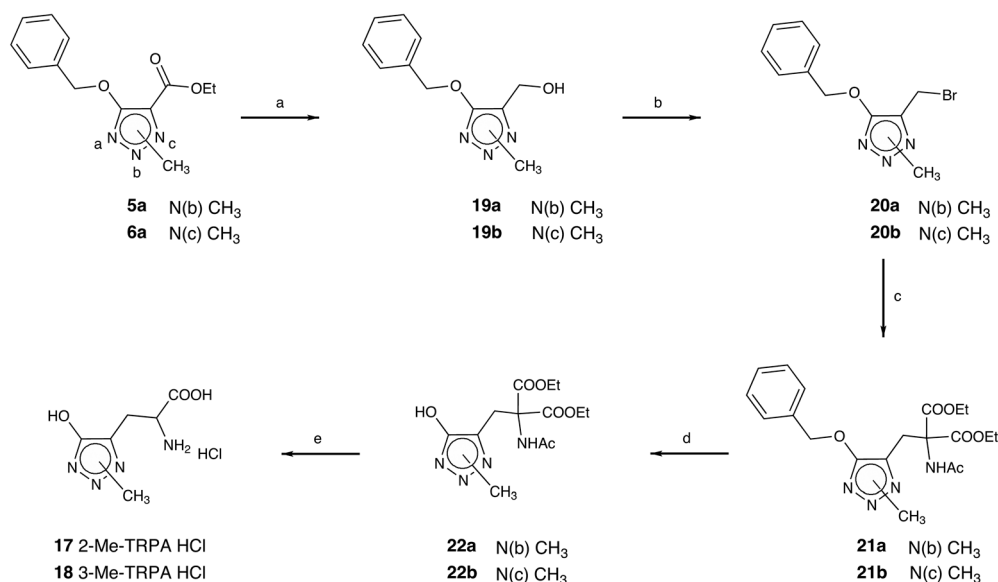
1) Targeting ionotropic AMPA GluRs using the hydroxytriazole moiety as a bioisosteric replacement. (*S*)-Glu (Table 2) plays a major role in the transmission of excitatory signals in the central nervous system, and is implicated in *e.g.* epilepsy, pain, memory, excitotoxicity, and brain development.⁴ (*S*)-Glu exerts its effects through two types of receptors: ligand-gated ionotropic receptors (iGluRs) and G-protein-coupled metabotropic

Table 2 Receptor binding affinities at native rat iGluRs^a

Compound	Structure	IC ₅₀ (μM)		K _i (μM) NMDA receptors	Distal carboxylate or its mimic pK _a
		AMPA receptors	KA receptors		
(S)-Glu ¹⁶		0.34	0.38	0.20	4.2 ¹⁷
AMPA ¹⁸		0.039	>100	>100	4.8 ¹⁹
(+)-HFPA ¹³		0.11	18	13	3.48
(S)-TDPA ¹⁵		0.065	>100	>100 ^b	– not determined
17 (2-Me-TRPA)		3.1 [5.54 ± 0.09] ^c	>100	>100	6.11 ± 0.02 ^d
18 (3-Me-TRPA)		1.4 [5.87 ± 0.08] ^c	>100	>100	6.42 ± 0.01 ^d

^a AMPA, KA, and NMDA receptors were studied using [³H]AMPA, [³H]KA, and [³H]CGP 39653 as radioligands, respectively. ^b [³H]CPP binding.

^c Mean pIC₅₀ ± SEM (shown in brackets) and the corresponding IC₅₀ values were calculated from full concentration-response curves of three individual experiments. ^d Determined by potentiometry (see ESI).



Scheme 2 Synthesis of AMPA GluRs agonists **17** and **18**; (a) NaBH₄, absolute ethanol, rt; (b) NBS, PPh₃, dry CH₂Cl₂, 0 °C; (c) NaH, diethyl acetamidomalonate, dry THF, rt; (d) H₂/Pd, dry THF, rt; (e) 6 N HCl, reflux.

receptors (mGluRs).¹³ iGluRs are classified, depending on their selective agonists, into NMDA (*N*-methyl-D-aspartate), AMPA ((*RS*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid, Table 2) and KA (kainic acid) receptors. The second class, mGluRs, are divided into three groups (I, II, III), each containing at least two subtypes. The vast majority of both iGluR and mGluR subtypes are considered to be interesting therapeutic targets for the treatment of a number of neurologic and psychiatric diseases. Specific agonists and antagonists are necessary to characterize the physiological roles of the individual receptors.¹² Since the late 1970s, the bioisosteric approach has been the strategy of election to design selective agonists and antagonists for AMPA/KA/NMDA receptors. In this connection, a number of bioisosteric replacements of the distal Glu carboxylic group have been reported. Among them, the authors recently presented (*R,S*)-2-amino-3-(4-hydroxy-1,2,5-oxadiazol-3-yl)propionic acid (HFPA, Table 2) as Glu analogue obtained using the hydroxy-1,2,5-oxadiazole scaffold.¹³

In an attempt to enhance selectivity for AMPA GluRs, the hydroxytriazole scaffold was used to bioisosterically replace the distal group of Glu. From a preliminary comparison between the pK_a values of the ethylcarboxylate 4-hydroxytriazole derivatives 2a and 3a and the Glu biosiosteres 17 and 18, we observed that replacement of the electron withdrawing carboxyl substituent entails an increase of pK_a (see Tables 1 and 2). In both isomeric methyl analogues, 2-Me-TRPA 17 and 3-MeTRPA 18, the pK_a values of the hydroxytriazole moiety were 6.11 and 6.42 respectively and an increase of 0.9 was measured *versus* 2a and 3a respectively. When the hydroxyfurazan series was studied, we observed an increase of pK_a of 0.24, as depicted in Tables 1 and 2 (derivatives 16 and (+)-HFPA). The extent of this effect depends on the hydroxyl substituted heterocycle and, being the furazan a strongly electron-acceptor group,¹⁴ a weaker effect on the acidic properties was observed. On the basis of these results, derivatives 17 and 18 more closely mimic the distal carboxylic acid of Glu, maintaining the correct degree of deprotonation of the hydroxyl group. Moreover, the hydroxytriazole scaffold also provides the opportunity of placing a small lipophilic portion oriented in two different directions, being useful for increasing the potency and/or selectivity towards a receptor subtype. It is known that AMPA GluRs present lipophilic cavities close to the distal carboxyl group in contrast to other Glu receptor subtypes. The *N*-methyl groups in both 17 and 18 are directed in well-defined areas within the Glu receptor binding site, unlike other examples, such as TDPA¹⁵ or HFPA, where unsubstituted ring systems have been used to mimic the distal carboxyl group.

The synthetic preparation of compounds 17 and 18 is shown in Scheme 2.

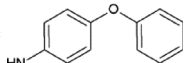
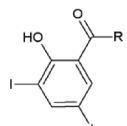
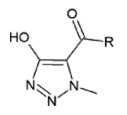
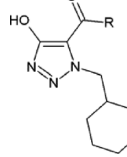
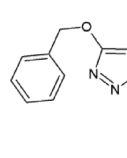
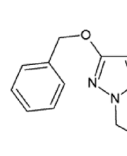
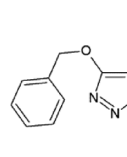
Compounds 5a or 6a were first reduced to their corresponding alcohols 19a–b (64% and 81% yield, respectively) and subsequently reacted with *N*-bromosuccinimide (NBS) to yield 20a (90% yield) and 20b (93% yield), respectively. Reaction with diethyl [(*tert*-butoxycarbonyl)amino]malonate in the presence of NaH (70% yield in both cases) followed by catalytic hydrogenation at atmospheric pressure furnished

hydroxytriazoles 22a (95% yield) and 22b (85% yield). Final deprotection of 22a and 22b in 6 N HCl at reflux gave hydrochloride salts of desired compounds 2-Me-TRPA (17) and 3-Me-TRPA (18) in quantitative yields.

The preliminary pharmacological results concerning iGluR receptor subtypes are shown in Table 2. Both 17 and 18, tested as racemic mixtures, present good selectivity within their receptor subtypes. In particular, both compounds presented a pharmacological profile quite similar to that of AMPA, as neither compound showed any activity on KA or NMDA receptors. The binding affinity of 18 toward the AMPA receptor was expected, as the AMPA receptor is capable of accommodating bulky groups in the area adjacent to the aminoacidic function. At the same time, if compared with AMPA, HFPA and TDPA, the low pK_a value of the hydroxytriazoles should be behind the low activity showed by these compounds. On the other hand, the *N*(b) substituted 2-Me-TRPA (17) analogue presented a quite interesting activity profile. In recent years, it was investigated the possibility to replace the 3-hydroxyisoxazole in AMPA with other isosters being able to extra substitute the ring and by effect to poses lipophilic bulkiness in a topographic receptor space. Recently, it was the case of 3-hydroxypyrazole AMPA analogue²⁰ (cpd6 in the reference) able to weakly but selectively inhibit AMPA receptor with IC_{50} of 8.9 μ M. This quite poor result was explained by the author with the increased pK_a value of the 3-hydroxypyrazole compared to the 3-hydroxyisoxazole in AMPA. 2-Me-TRPA (17) analogues, showing a lower pK_a value of hydroxypyrazole cpd6,²⁰ was found able to selectively inhibit AMPA receptor with IC_{50} of 3.1 μ M, being almost three time more active than cpd6.²⁰ This preliminary quite interesting results will open the possibility to design subtype selective ligands by insertion of substituents on the *N*(b) triazole position that may reach non-conserved regions of the receptor.

2) **Targeting OvCHT1 using the hydroxytriazole moiety within a scaffold hopping approach.** *Onchocerciasis*, also known as river blindness, is a neglected tropical disease caused by the parasitic worm *Onchocerca volvulus* (*O. volvulus*), and is the world's second leading infectious cause of blindness. An estimated 37 million people are infected with river blindness, mostly in developing countries, in sub-Saharan Africa and Central and South America.²¹ Additionally, the possible emergence of Ivermectin-resistant *O. volvulus* accelerates the need to develop new innovative therapeutic strategies in this field, since the broad-spectrum antiparasitic drug Ivermectin is the product currently most widely used to treat the disease.²² OvCHT1 is a larval-stage-specific chitinase that was recently identified as a potential biological target affecting nematode development.²³ As a result of a blind screening program, Closantel was discovered to be a potent and selective inhibitor of OvCHT1. Starting from this lead, a series of Closantel analogues was prepared to afford chitinase inhibitors with IC_{50} values in the low nanomolar range.⁵ Of these, compound MDG-1-33A (Table 3) was found to inhibit OvCHT1 with an IC_{50} value of 1.98 μ M.⁵ Using a scaffold hopping approach, the diiodophenolic core,

Table 3 IC₅₀ of OvCht1 inhibition

Compound	Structure R = 	IC ₅₀ (μM) ^a
MDG-1-33A		1.98 ⁵
23		4.69 ± 0.29
24		5.11 ± 0.06
25		0.52 ± 0.03
26		0.41 ± 0.01
27		0.41 ± 0.04

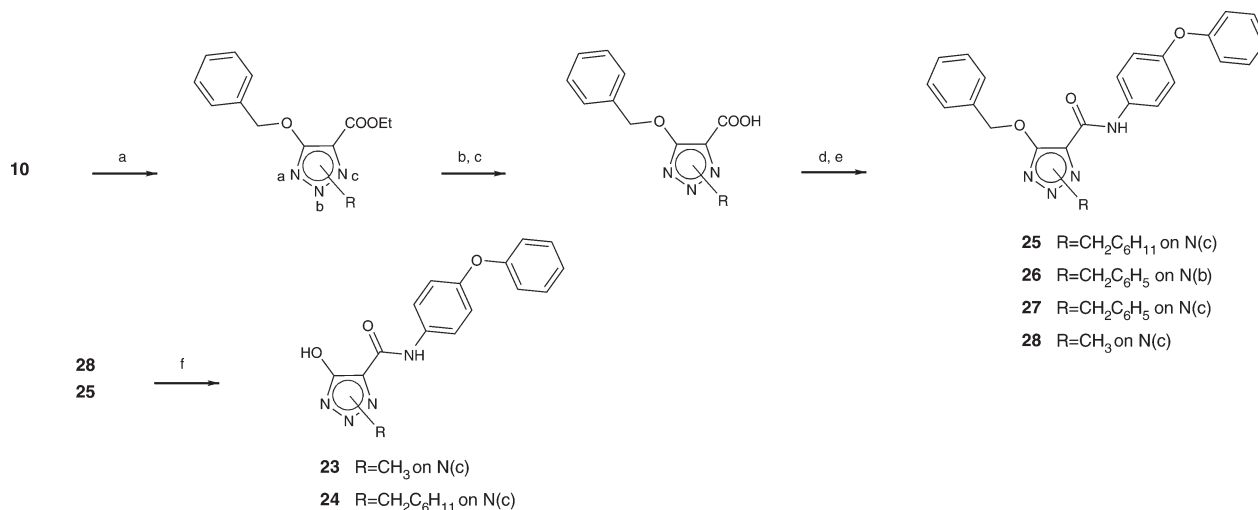
^a *In vitro* OvCht1 inhibition activity was measured by fluorescence-based assay (see ESI).²³ Each dataset represents mean ± SD of three independent assays.

found to be essential for chitinase inhibition, in MDG-1-33A was replaced by the hydroxytriazole scaffold to give derivatives 23–27. The synthetic routes for the preparation of compounds 23–27 are outlined in Scheme 3. Alkylation of compound 10 produced two isomers, which were separable by flash chromatography. As previously discussed, compounds with alkyl substituent on the N(b) atom were obtained in higher amounts (range: 45–50% yield) than compounds with alkyl substituent on the N(c) atom (range 15–30% yield). Basic hydrolysis yielded the carboxylic acid (around 90% yield in all cases), which was subsequently converted into the corresponding acyl chloride. Reaction with 4-phenoxyaniline yielded compounds 25–28 (40–65% range of yield). Catalytic hydrogenation of 28 and 25 afforded hydroxytriazoles 23 and 24 respectively, in quantitative yields.

During the subsequent fine tuning modulation of the hydroxytriazole scaffold (data not shown), the role of four possible substitutions on the triazole ring was determined considering all the N(a), N(b) and N(c) positions. Because of the fact that the phenolic group in MDG-1-33A analogues can be successfully alkylated without affecting chitinase inhibition, the O-alkylated triazole analogues were also considered. From these studies, it was found that the presence of either N(b) or N(c) alkyl substituents is beneficial to the potency that follow the size of the alkyl substituent. The combination of these facts together with the presence of a benzyl substituent on the hydroxyl group afforded submicromolar range compounds. IC₅₀ values of MDG-1-33A triazole derivatives 23–27 are shown in Table 3. The results of these scaffold hopping procedures afforded three promising MDG-1-33A derivatives, compounds 25, 26 and 27, that inhibit OvCht1 chitinase in the nM range.

Conclusions

We have described the preparation of N-substituted hydroxytriazoles, as possible bioisosteres of the carboxylic functionality.



Scheme 3 Synthesis of OvCht1 chitinase inhibitors 23–27; (a) R-X, K₂CO₃, CH₃CN, rt; (b) 2 N LiOH, THF, rt; (c) 2 N HCl, H₂O; (d) (COCl)₂, DMF, dry THF; (e) 4-phenoxyaniline, dry pyridine, dry THF, rt; (f) H₂/Pd, dry THF, rt.

Synthetic strategies, spectral characterization of representative compounds, as well as the experimental acquisition of the dissociation constants (pK_a) of *N*-methyl- and *N*-benzylhydroxytriazoles, are reported. Our results provided a new data set of possible carboxylic acid mimics based on the hydroxytriazole scaffold with pK_a values in the 5.14–6.71 range and $C\log P$ values ranging from 0.46 to 2.72. This information might facilitate their application within a bioisosteric approach to drug design. Two preliminary bioisosteric applications of these new hydroxytriazole-based isosteres of the carboxyl group are described: the first is an example of classical bioisosteric modulation in which the carboxylic acid of a lead compound is fine-tuned; in the second example, this moiety was explored *via* scaffold hopping replacement of the phenol ring present in a lead compound bearing a salicylamide-type structure. Detailed description of this research, together with other bioisosteric applications currently under study, will be the subject of forthcoming publications.

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